

## **REMARKS/ARGUMENTS**

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

Claim 1 has been amended to require in step (a) that the human blood comprise CD4<sup>+</sup> CD25<sup>+</sup> regulatory T cells. This was implicit in step (a) in view of the preamble and step (b), but has now been made explicit. Claim 1 has also been amended to correct the reference to “CTLA-4” and to delete the “wherein” clause. Claim 4 has likewise been amended to correct the reference to “CTLA-4.” Applicants do not believe that any of these amendments introduce new matter. An early notice to that effect is earnestly solicited.

Claims 12 and 24-32 were rejected under 35 USC § 112, first paragraph, as claiming new matter. In response, Applicants have deleted the previously introduced limitation “wherein no stimulation with cytokines or dendritic cells is performed between the steps” without prejudice. In view of this amendment, Applicants respectfully submit that this rejection is overcome.

Claims 12 and 24-32 were rejected under 35 USC § 103(a) as being obvious over Jonuleit et al. (“Jonuleit”), *J. Exp. Med.*, 192: 1213-1222 (2000), in view of Takahashi et al. (“Takahashi”), *J. Exp. Med.*, 192: 303-309 (2000). In response, Applicants respectfully submit that the cited combination of references fails to make out a *prima facie* case of obviousness. Assuming for the sake of argument that the cited combination of references did make out a *prima facie* case of obviousness, the present invention is characterized by unexpected results, which are, therefore, objective evidence of nonobviousness. Consequently, for either reason, the Examiner would be fully justified to reconsider and withdraw this rejection.

With respect to the issue whether a *prima facie* case of obviousness has been made out, Applicants respectfully submit that the cited combination of Jonuleit and Takahashi fails to teach or suggest that human blood comprises CD4<sup>+</sup> CD25<sup>+</sup> regulatory T cells, as required by step (a) of instant claim 12. Although Takahashi teaches that a CD4<sup>+</sup> CD25<sup>+</sup> T cells population was known to exist in *mice*, it was unknown prior to the present invention whether such a population of CD4<sup>+</sup> CD25<sup>+</sup> regulatory T cells also existed in humans. Without such knowledge, a person having ordinary skill in the art would not have found it *prima facie* obvious, as required by step (a) of instant claim 12, to contact human blood comprising such cells with ligands specifically binding to CD4 and CD25 and/or CTLA-4 entities on the T cells. Nor would such a person, lacking the knowledge that human blood contained such CD4<sup>+</sup> CD25<sup>+</sup> regulatory T cells, have had any reasonable expectation that by performing step (a) on human blood it should be possible to successfully identify, monitor and/or remove CD4<sup>+</sup> CD25<sup>+</sup> regulatory T cells from the human blood.

The Examiner says that Jonuleit discloses a method of identifying, monitoring and/or removing CD4<sup>+</sup> CD25<sup>+</sup> T cells from human blood. However, Applicants respectfully submit that the Examiner's reading of Jonuleit is incorrect. Jonuleit teaches that naïve CD4<sup>+</sup> T cells were purified from cord blood or peripheral blood (see the last paragraph on page 1214), *and then* T cells having the CD25<sup>+</sup> phenotype were generated *only* after priming and repeated stimulation with immature or mature dendritic cells (see the second sentence on page 1215 and the second paragraph on page 1216.) In other words, Jonuleit does not teach that the human blood comprised CD4<sup>+</sup> CD25<sup>+</sup> regulatory T cells, as required by step (a) of instant claim 12. Rather, Jonuleit teaches the human blood comprised naïve CD4<sup>+</sup> T cells that could be induced *artificially*

to exhibit the CD4<sup>+</sup> CD25<sup>+</sup> phenotype *after* purification from the blood by priming and repeated rounds of *ex vivo* stimulation with immature or mature dendritic cells.

In short, while Takahashi teaches that a population of CD4<sup>+</sup> CD25<sup>+</sup> regulatory T cells exists in *mice*, Takahashi is completely silent about whether a corresponding population exists in humans or in human blood. Further, while Jonuleit teaches that a population of human CD4<sup>+</sup> CD25<sup>+</sup> T cells can be induced artificially *ex vivo*, Jonuleit is also silent about whether such population exists naturally in humans or in human blood. There is, thus, nothing in the combination of Jonuleit and Takahashi that would have led a person having ordinary skill in the art to expect that a population of CD4<sup>+</sup> CD25<sup>+</sup> regulatory T cells exists naturally in humans or in human blood or, therefore, that by contacting human blood with ligands specifically binding to CD4<sup>+</sup> and CD25<sup>+</sup> and/or CTLA-4 it should be possible to successfully identify, monitor and/or remove such T cells from the human blood.

In view of the foregoing, Applicants respectfully submit that the combination of Jonuleit and Takahashi fails to make out a *prima facie* case of the obviousness of the instant claims. Therefore, Applicants also respectfully submit that the Examiner can reconsider and withdraw this rejection on this basis alone.

As an additional or alternative basis for patentability, Applicants additionally submit that the present invention is clearly characterized by an unexpected result, which is, therefore, objective evidence of nonobviousness. In this regard, Applicants call the Examiner's attention to the paragraph bridging pages 3-4 of the instant specification. As discussed at page 3, lines 25-30, T cells exhibiting the CD4<sup>+</sup> CD25<sup>+</sup> were apparently known for over a decade prior to the present

invention, but were *misinterpreted as being conventional memory cells*. All that time, those skilled in the art had been searching for the human counterpart of murine CD4<sup>+</sup> CD25<sup>+</sup> regulatory T cells, yet until the present invention no one had been able to identify the human counterpart cells. Surprisingly, and quite unexpectedly, Applicants discovered these human counterparts to exist as cells that the art had determined were actually of a different character. This is a remarkable, surprising and unexpected discovery in the face of established art prejudice, and a discovery that greatly advances the knowledge in the art and is deserving of patent protection. Applicant's surprising discovery, in the face of an established prejudice in the art that these cells were of a different character, is clearly an unexpected result of clear practical import, which is, therefore, proof of nonobviousness.

In view of the foregoing, Applicants respectfully submit that the Examiner can justify the allowance of this application on this clearly demonstrated unexpected result. An early notice that this rejection has been reconsidered and withdrawn is, therefore, earnestly solicited.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,

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